REMARKS

Claims 9-15 and 17-25 are pending. Claims 9, 14, 17 and 20 have been amended. Claims 9 and 14 have been amended to clarify that Applicants are claiming an oral composition. Claims 17-24 were previously withdrawn by the Examiner. However, claims 17 and 20 are dependent on claim 9 and have been amended to conform to the amendments to that claim. Applicants request rejoinder of these dependent method claims upon allowance of the product claims. No new matter has been added.

Rejections Under 35 USC §103

Applicants are grateful for the withdrawal of the rejection of Claims 9-10 under 35 U.S.C. 103(a) for alleged obviousness over Lopresti et al, J. of Clinical Endocrinology and Metabolism, Vol. 73, No. 4, 1992, pages 703-709 ("Lopresti") in view of Miura US 5,116,828 ("Miura").

Rejection of Claims 9-15 and 25 Under 35 USC §103 Over Santini et al. in View of Miura

Claims 9-15 and 25 were rejected for alleged obviousness over Santini et al., Thyromimetic Effects of 3,5,3"-triiodothyronine Sulphate in Hypothyroid Rats, Endocrinology 133(1): 105-110 (1993) ("Santini") in view of Miura. The Examiner states that Santini discloses treatment of thyroidectomised rats with T3S and T3 via intraperitoneal injection. The Examiner admits "[a]lthough Santini et al. teach formulations comprising T_3S this reference does not teach compositions comprising T_3S in the specific instantly claimed amount of 5 to 1000µg. Further, Santini et al. do not teach the instant claimed combination of T_3S and thyroxine." OA, p 7-8. However, the Examiner asserts that it would have been obvious "to manipulate the dosage amount of T_3S in the composition taught by Santini et al.,…based on patient parameters such as age, weight and severity of condition." Further, the examiner asserts that it would have been obvious to use Applicants claimed dosage range and thyroxine (T_4) in view of Miura's disclosure of T_3 and T_4 dosage ranges." One would have been motivated to do so because T_3S as taught by Santini et al. and T4 as taught by Miura et al. are thyromimetic agents…" OA at 8.

Applicants respectfully traverse. In order to establish obviousness, it is necessary, *inter alia*, to (i) determine the scope of the prior art and (ii) the differences between the claimed

subject matter and that of the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Applicants point out that in order to establish a *prima facie* case of obviousness, the examiner must provide a showing that, *inter alia*, the cited prior art references teach or suggest all of the claim limitations and there is some suggestion or motivation to combine the references. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); MPEP §§2142 and 2143. Furthermore, a *prima facie* finding of obviousness cannot be established when the "improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct 1727, 1739 (2007). Lastly, a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. (MPEP 2144.09).

The Cited References Do Not Teach or Suggest an Oral Composition of T_3S

Applicants respectfully submit that a prima facie case of obviousness has not been established. Santini is directed exclusively to the **intraperitoneal** injection of T_3S and the thyromimetic activity discussed resulted only from such intraperitoneal administration. Santini neither teaches nor suggests an oral composition. Miura fails to remedy this deficiency. As acknowledged by the Examiner, Miura is directed to dosages of T_3 and T_4 and neither teaches nor suggests that T_3S is a thyromimetic let alone that it may be used in an oral composition. Thus, the cited combination of references fails to disclose each and every element of the claimed invention and a prima facie case of obviousness has not been established.

Applicants submit that the failure of the cited references to teach or suggest an oral composition precludes a finding of obviousness. Due to the significant differences in drug metabolism and bio-distribution between a composition that is injected i.p. and an oral composition, the former cannot be deemed to suggest the latter. This is especially true where, as here, the only prior art reference to address oral T_3S (albeit radiolabled T_3S), taught that T_3S was an inactive metabolite which was presumably not absorbed by the GI system upon oral administration. Thus, one skilled in the art believing T_3S exerted possible thyromimetic activity based on Santini and aware of Lopresti, as well as the highly polar nature of T_3S, would have **no** expectation that T_3S would be properly absorbed upon oral ingestion so as to act as an oral thyromimetic drug. Consequently, the combination of Santini with any of the cited references

would teach the skilled artisan that only by **intraperitoneal** administration could one expect any thyromimetic activity from T_3S.

Applicants note that the Examiner has requested conversion of the nanomolar i.p. dosage disclosed in Santini to micrograms so that it may be compared to the instant claims. Applicants submit that this comparison is improper as, for the reasons set forth above, the i.p. rat dosage of Santini is irrelevant to instantly claimed oral human composition. However, to be responsive, Applicants have converted the dosage of Santini to a human dosage in micrograms and submit that the instantly claimed oral composition is effective at much lower doses than the i.p injections required by Santini.

Santini teaches that high doses of T_3S are preferable and more effective (see pages 108-109) and discloses administration of a maximum of 11.5 nmol T_3S **i.p.** per rat per day. See Santini p. 107, 3 day experiment. T_3S has a molecular weight of 729; thus 729 ng corresponds to 1 nmol. Consequently Santini's dose of 11.5nmol i.p per rat per day equals 8.89 μg/ rat per day. To convert this to a human dosage, we will assume that Santinis's rats weigh about 0.2 kg (see Experimental Procedure, p. 105, where the weights range from 0.18-0.2 kg) and a human subject has an average weight of 70kg. Thus, Santini's dosage of 11.5 nmol/day is equivalent to a human dosage of 2930 μg (2.93 mg) per day, significantly higher than the instantly claimed oral composition dosage.[1]

In sum, as Lopresti, the only cited reference which actually investigated the thyromimetic activity and metabolism of **oral** T3S (albeit radiolabeled T3S), showed it would not be clinically active upon oral administration, and the remaining references neither teach nor suggest an oral composition of T_3S, the cited combination of references fails to disclose each and every element of the claimed invention and a prima facie case of obviousness has not been established.

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[1] Applicants note that Santini discloses several lower i.p. dosages of T_3S (e.g. 2.3 nmol/day and 0.46 nmol/day). However, given the statement at page 108 that the magnitude of the ameliorative effects of T_3S "was dependent on the duration of the treatment and the amount of T3S injected.." it appears that the largest Santini dosage was the most preferred. Moreover, even the 2.3 nmol/day dosage discussed in Santini (which corresponds to a human i.p. dosage of 588 μg) is significantly higher than the maximum dose of 160μg of the T_3S oral composition of the invention administered to human subjects in the clinical trials performed by Dr. Pinchera. See Rule 132 Declaration of Dr. Aldo Pinchera, ¶ 5.

The Claimed Oral Compositions Have Unexpected Advantages Over the Cited References

Applicants submit that the instant claims are not obvious over the cited references for the additional reason that the claimed invention has unexpected advantages over the cited references. As an initial matter oral compositions are significantly easier to administer and more convenient than compositions like those of Santini requiring injection i.p. Moreover, as shown by the Rule 132 Declaration of Dr. Aldo Pinchera ("Pinchera Declaration") submitted herewith, the oral compositions of the invention were absorbed by the gastrointestinal system and metabolized to the active T_3 when administered to human subjects at doses of 20-160 μg of T_3S. This data is unexpected in view of the teaching of Lopresti, discussed supra, that oral radio-labelled T_3S was inactive and presumably not absorbed by the GI tract.[2] It is also unexpected in view of the large dosages of T_3S (e.g. 2930 μg) Santini discloses for **i.p.** administration.

Specifically, as Dr Pinchera explains 28 human subjects with surgically excised thyroids were administered a single dose of an oral composition of the invention containing 20, 40, 80 or 160 μg of T_3S. The gastrointestinal absorption of T_3S was assessed by serum levels of thyroid hormone including T_3S and triiodothyronine ("T_3") as both free T_3 ("FT_3") and total T_3 ("TT_3"). Subjects without thyroid glands have no endogenous thyroid hormone production; thus any measured thyroid hormone was due to the administered oral compositions. Pinchera Declaration, ¶ 5.

As shown in Figure 1 of the Pinchera Declaration, all subjects, regardless of dose, exhibited gastrointestinal absorption of the oral composition as shown by detection of T_3S in serum with a peak level two hours after administration of the oral composition. Pinchera Declaration, ¶ 6, 24.

In patients lacking a thyroid there is no endogenous T_3. Thus, all T_3 present in the subjects was the result of conversion of T_3S from the oral compositions to T_3 in vivo. By monitoring serum T_3S and TT_3 levels after administration of the oral T_3S compositions, it was determined that T_3S serum level are maintained for at least 48 hrs (Fig 1 and 2) and that it was converted to the clinically active TT_3 in a dose related fashion. Pinchera Declaration, ¶ 7, 25; Figure 2.

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[2] Applicants note that the Pinchera Declaration reports data from a clinical trial concluded in February 2010; thus it is timely.

These results were unexpected given the teaching of Lopresti that radio-labelled T_3S was not clinically active upon oral administration, Pinchera Declaration, ¶ 8, 26, and given the high dosages of **i.p.** T_3S taught by Santini.

In sum, Applicants submit that the instant claims are not obvious over the cited references for the additional reason that the claimed oral compositions have advantages which were unexpected in light of the teachings of Lopresti, Santini and the other cited references.

CONCLUSION

In view of the preceding remarks, it is believed that claims 9-15 and 25 are in condition for allowance. Applicants request rejoinder of claims 17-24.

If there are any questions remaining as to patentability of the pending claims, Applicants would very much desire to have a telephonic interview. The Examiner is invited to contact Applicants' undersigned attorney at the number below.

No fee is believed to be due with the filing of this Amendment other than the fee for the three month extension of time. However, if any additional fees are deemed necessary, the Director is hereby authorized to charge such fees to Deposit Account No. 50-2168.

Favorable action is respectfully requested.

Respectfully submitted,

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